

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2005/000348

International filing date (day/month/year)
01.02.2005

Priority date (day/month/year)
03.02.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/505, A61P11/00, A61P37/00, A61P29/00

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/GB2005/000348

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/GB2005/000348**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 1,2,4-6 (IA only);1-5 (in part)

because:

- ☒ the said international application, or the said claims Nos. 1,2,4-6 (IA only) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-5(in part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-7
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-7
Industrial applicability (IA)	Yes: Claims	3,7
	No: Claims	1,2,4-6

2. Citations and explanations**see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)**see form 210**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2005/000348

1. Section III

1.1 Claims 1, 2 and 4-6 are directed to a method of treatment of the human/animal body by therapy. Such subject-matter is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, and therefore no opinion shall be formulated with respect to industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). However an opinion shall be formulated with respect to novelty and inventive step based on the alleged effects of the compounds/compositions.

1.2 The expression "a condition mediated by the activity of CB2 receptors or a condition which is mediated by a PDE4 inhibitor" is so vague and unclear that no search of it could be carried out. The search has therefore been limited to combinations of CB2 ligands and PDE4 inhibitors for the treatment of the diseases listed in claim 6.

2. Section V

2.1 Cited Documents

The following documents (D) are referred to in this Opinion; the numbering will be adhered to in the rest of the procedure:

- D1: FR-A-2 839 718 (SANOFI-SYNTHELABO) 21 November 2003
- D2: WO 02/060447 A (UNIVERSITY OF CONNECTICUT; MAKRIYANNIS, ALEXANDROS; DENG, HONGFENG) 8 August 2002
- D3: US-A-5 925 768 (BARTH ET AL) 20 July 1999
- D4: WO 97/09315 A (SIGNAL PHARMACEUTICALS, INC; SUTO, MARK, J; GOLDMAN, MARK, E; GAYO, LE) 13 March 1997
- D5: HUANG Z ET AL: "The next generation of PDE4 inhibitors." CURRENT OPINION IN CHEMICAL BIOLOGY., vol. 5, no. 4, 2001, pages 432-438, XP002325704
- D6: SOUNESS J E ET AL: "Immunosuppressive and anti-inflammatory effects of cyclic AMP phosphodiesterase (PDE) type 4 inhibitors." IMMUNOPHARMACOLOGY, vol. 47, no. 2-3, 2000, pages 127-162, XP002325705
- D7: WO 02/062750 A (SCHERING CORPORATION) 15 August 2002 (15)
- D8: WO 2004/000807 A (SCHERING CORPORATION; KOZLOWSKI, JOSEPH, A;

**WRITTEN OPINION OF THE
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International application No.

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SHANKAR, BANDARPALLE, B; S) 31 December 2003 (2003-12-31)

Unless otherwise indicated reference is hereafter made to the passages cited in the Search Report.

2.2 The prior art

FR 2 839 718 A: The document describes the use of CB2 ligands for the treatment of a number of diseases falling under the scope of present claim 6.

WO 02/060447 A: The document describes the use of CB2 ligands for the treatment of a number of diseases falling under the scope of present claim 6.

US 5 925 768 A: The document describes the use of CB2 ligands for the treatment of a number of diseases falling under the scope of present claim 6.

WO 97/09315 A: The document describes the use of molecules falling under the scope of present Formula III for the treatment of rheumatoid arthritis, osteoarthritis, ARDS and asthma. The molecules are however not identified as cannabinoid modulators.

XP002325704: The document discloses the uses of PDE4 inhibitors and lists some of them, including roflumilast and cilomilast

XP002325705: The document is a review of the biology and pharmacology of PDE4 inhibitors. It also lists some of the most recent ones, including D4418, CI1018 and V11294, and diffusely treats the diseases that can be treated with them.

WO 02/062750 A: The document suggests the possibility of combining cannabinoid agonists with PDE4 inhibitors

WO 2004/000807 A: The document suggests the possibility of combining cannabinoid agonists with PDE4 inhibitors

2.3 Art 33(2) PCT (Novelty)

The subject-matter of claims 1-7 of the present application meets the requirements of Article 33(2) PCT.

None of the cited documents discloses combinations of CB2 ligands and PDE4 inhibitors, nor their use in pharmacy.

**WRITTEN OPINION OF THE
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2.4 Art 33(3) PCT (Inventive step)

The subject-matter of claims 1-7 of the present application does not meet the requirements of Article 33(3) PCT.

The uses in medicine of CB2 ligands and PDE4 inhibitors are known in the art, as documents D1-D6 clearly show. No inventiveness can be seen in combining agents that individually are active in the treatment of certain diseases in order to obtain a combination which treats the same diseases, the more so since no unexpected or surprising effect results from the combination. Such a combination is even suggested in documents D7 and D8.

In this context it is observed that the application as a whole does not disclose any synergistic effect. Any supplementary data provided later in order to show the presence of such effect, while possibly providing a proof of the presence of an inventive step, will render the application as filed insufficiently disclosed (Art 5 PCT), a fact that cannot in any way be remedied. In any case, the present application describes a potentially infinite number of possible combinations, not all of which will be synergistic, if at all. No indication is however provided in the application as filed as to how the skilled person could identify those that show synergy, one more reason why the present application does not disclose at all a synergistic effect. One final observation in this respect is that the wording of claim 1 ("a condition mediated by the activity of CB2 receptors or a condition which is mediated by a PDE4 inhibitor") seems in any way to exclude the presence of such an effect, and that rather the application aims at protecting the use of a combination of agents for treating an alternative list of diseases, where the two agents do not interact in any way among them. In this case it is not foreseeable how inventive step could at all be established.

2.5 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 1, 2 and 4-6 are industrially applicable since their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

2. Section VI

Other cited documents (Rule 70.10 PCT)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2005/000348

Patent number	Filing date	Priority date	Publication date
WO2004/018433	19.08.03	21.08.03	04.03.04
WO2004/018434	19.08.03	21.08.02	04.03.04
WO2004/029026	25.09.03	27.09.02	08.04.04
WO2004/029027	25.09.03	27.09.02	08.04.04
WO2004/085385	18.03.04	20.03.02	07.10.04

WO 2004/018433 A: The document discloses the CB2 modulators of present Formula III for the treatment of the diseases of present claim 6

WO 2004/018434 A: The document discloses the CB2 modulators of present Formula III for the treatment of the diseases of present claim 6

WO 2004/029026 A: The document discloses the CB2 modulators of present Formulas I and II for the treatment of the diseases of present claim 6

WO 2004/029027 A: The document discloses the CB2 modulators of present Formulas I and II for the treatment of the diseases of present claim 6

WO 2004/085385 A: The document discloses the use of a combination of cannabinoid ligands and PDE4 inhibitors for the treatment of rheumatoid arthritis